Lupus Nephritis

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Outline

- Epidemiology
- Pathophysiology
- Histological Classifications
- Therapy
- Future Directions

Epidemiology

- SLE incidence: approx. 1 in 500 in the U.S.
- Prevalence: 4-250 per 100,000
- Female/Male: 9/1.
- Age: peak incidence in 30s.
- Race: Black > White.
- Pediatric vs adult rates of renal involvement approx. the same.

Epidemiology (cont.)

- Clinical evidence of renal disease: 35-90% of all SLE.
- Light microscopy abnormalities: 90%.
- Electron microscopy/Immunofluorescence abnormalities: approaches 100%.

Epidemiology (cont..)

- USRDS: 3900 cases of ESRD from SLE between 1991-1995 (1.3% of total).
- 80% female.
- 50% white, 43% black, 5% Asian.

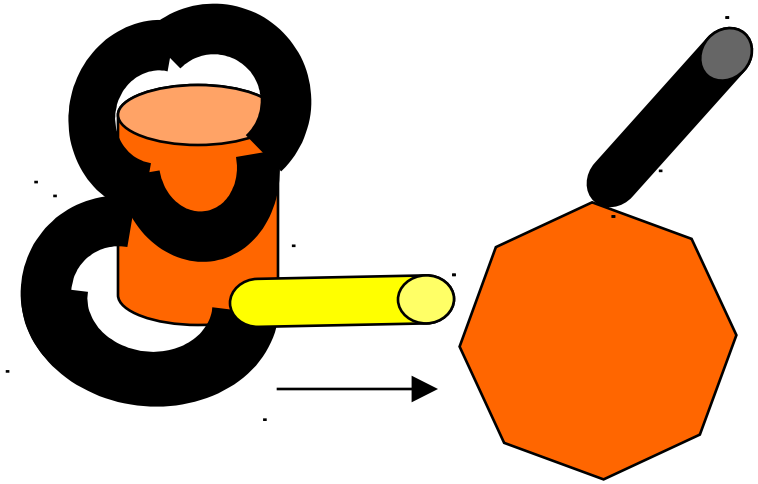
Pathophysiology

- Originally proposed as the prototypical immune-complex disease (Koffler *et al*., 1971).
- Cardinal feature is presence of Ig and C deposition in mesangium or mesangium + capillary.
- First believed to result from deposition of circulating DNA/anti-DNA complexes; this theory now mostly discounted.

Pathophysiology (cont.)

- Anti-DNA Ab can bind to many other antigens: GBM (heparan sulfate, laminin), endothelial and mesangial cells.
- Nucleosomes (DNA+histone) are believed to mediate binding of anti-DNA Ab

The Nucleosome



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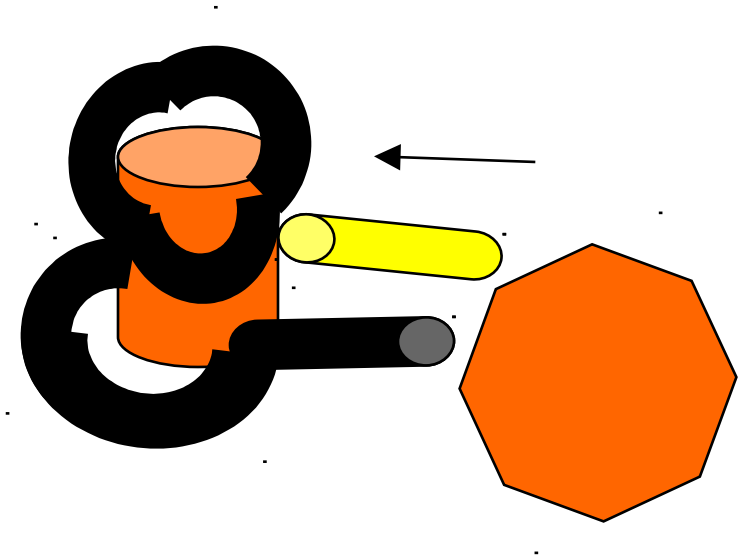
Adapted from **Mechanism of Transcription Through the Nucleosome by Eukaryotic RNA Polymerase**. Studitsky, Vasily M.; Kassavetis, George A.; Geiduschek, E. Peter; Felsenfeld, Gary. Science, Volume 278(5345) December 12, 1997 pp 1960-1963

The Nucleosome



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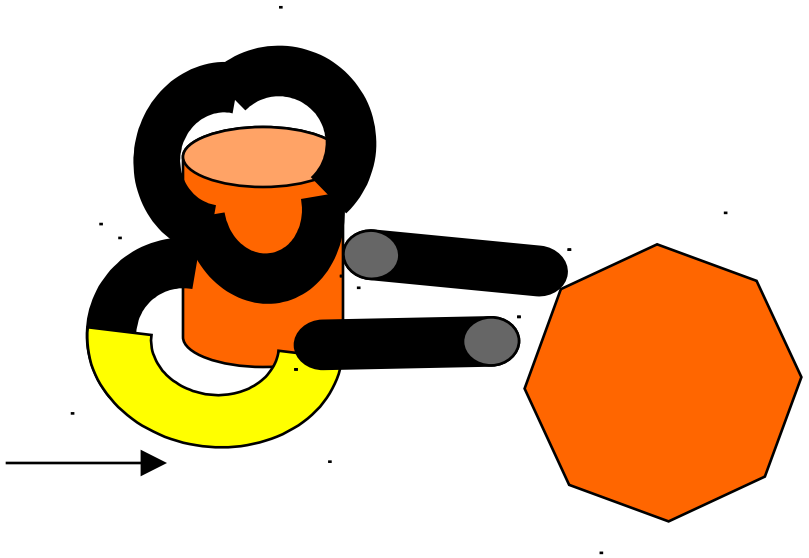
The Nucleosome



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Nucleosomes and Apoptosis

- Nucleosomes (along with extractable nuclear antigens [ENA]) are found in apoptotic bodies.
- Apoptotic cells normally phagocytosed by macrophages or parenchymal cells.
- Disturbance in apoptosis/phagocytosis balance may be associated with increased levels of circulating nucleosomes/ENA.

Nucleosomes and Apoptosis (cont..)

- Altered apoptosis may be a mechanism in the MRL/lpr mouse (spontaneous lupus model).
- Increased soluble Fas and overexpression of bcl-2 gene (inhibitors of apoptosis) and increased *in vitro* apoptosis in humans may link autoimmunity and lupus.

Nucleosomes and Apoptosis (cont.)

- Impaired apoptosis can lead to persistence of autoreactive T-cells.
- Circulating nucleosomes may eventually be chemically altered, causing activation of T-helper cells.

Nucleosomes and Autoimmunity

- Nucleosomes are believed to also to be the autoantigens responsible for initiating the autoimmune response in SLE.
- Anti-nucleosome antibodies are increasingly reported in SLE and may precede other anti-nuclear Ab.
- The autoimmune response is believed to be T-cell mediated.

Nucleosomes and GN

- Rats infused with anti-nuclear Ab/nucleosome complex developed GBM-bound complexes, while Ab infused without nucelosomes did not (Kramers *et al*., 1994).
- The key GBM binding site appears to be heparan sulfate. Collagen IV also can bind.

Nucleosomes and GN (cont.)

- Nucleosome/Ab complex titers correlate with the presence of lupus nephritis in both experimental and clinical studies (Bernstein et al., 1993 and 1994).
- Use of heparin (analogue of heparan sulfate) in mice inhibited immune deposition and reduced GN and albuminuria (van Bruggen et al., 1996).

Nucleosomes and GN (cont.)

- Immunofluorescence microscopy with nucleosome- and histone-specific monoclonal antibodies can be used to find nucleosomes in glomerular deposits

WHO Class I: Normal

- LM, EM, IF all normal
- Rare incidence

WHO Class II: Mesangial

- LM: mesangial widening or mild hypercellularity
- EM, IF: mesangial deposits, +/- subendothelial deposits
- Subclass A/B depending on degree of hypercellularity

WHO Class II (cont.)

- 10-20 % of cases
- Prognosis excellent
- No therapy indicated

WHO Class III: Focal proliferative

- LM: Diffuse mesangial hypercellularity, Focal/segmental necrosis and proliferation, hyaline thrombi
- EM: Mesangial and subendothelial deposits
- IF: Granular mesangial and capillary Ig, C3
- Subclassed depending on degree of necrosis and sclerosis

WHO Class III (cont.)

- 10-20% of cases
- Variable prognosis
- May represent one end of spectrum with Class IV
- Prognosis: with < 25% of glomeruli involved, < 5% progress @ 5 years. With 40-50% involved, 15-25% progress to renal death @ 5 years.

WHO Class IV: Diffuse proliferative

- LM: Diffuse hypercellularity, mesangial and endocapillary proliferation, crescents, leukocytic infiltration
- EM: mesangial, subendothelial, subepithelial deposits
- IF: Mesangial and capillary Ig, C3. Extraglomerular deposits.
- Subclassed based on degree of necrosis and sclerosis

WHO Class IV (cont.)

- Most common form, around 40-50%
- Associated with worse prognosis: 5-year renal death rate 10-40%.
- Poor prognosis: African-American, Cr > 2.4 mg/dl, crescents, tubulointerstitial disease, vascular disease
- General indication for considering cytotoxic therapy

WHO Class V: Membranous

- LM: diffuse membranous thickening, mesangial prominence
- EM: Epi/intramembranous deposits, mesangial deposits
- IF: Peripheral granular IgG, C3

WHO Class V (cont.)

- Prognosis variable. May have partial or complete remission with stable creatinines for 5 years or more.
- Overall 5-year renal death rate 10-30%.
- Therapy generally recommended for florid nephrosis or deterioration in renal function.

WHO Class VI

- Characterized by completely or segmentally sclerotic glomeruli as primary abnormality.
- May be considered as either end-stage or arrested disease and not necessarily as separate class.

WHO Classes

- Transformation rate between classes: 10-40%.
- Any transformation possible.
- Most common Class III to Class IV.
- Also common: II to III, II to IV, III to V, IV to V.
- Not predictable from clinical presentation.

WHO Classes (cont.)

- Clinical presentation does not correlate with type or severity of glomerular lesion.
- No relationship between histology and serology.

Markers of active disease

- Endocapillary hypercellularity
- Leukocytic infiltration
- Subendothelial hyalin deposits
- Fibrinoid necrosis/karyorrhexis
- Cellular crescents
- Interstitial inflammation

Markers of chronic disease

- Glomerular sclerosis
- Fibrous crescents
- Tubular atrophy
- Interstitial fibrosis

Extraglomerular Disease

- Vascular
- Tubulointerstitial

Vascular Disease

- Hypertensive arterial lesions: intimal protein accumulation, endothelial cell damage, luminal narrowing or occlusion by precipitates
- Rarely, may have necrotizing vasculitis which may be assoc. with ANCA.
- May have poorer renal prognosis with vascular disease, mortality unchanged.

Tubulointerstitial Disease

- Mostly found with proliferative GNs.
- May see deposits in tubule basement membrane, interstitium, peritubular capillaries, Bowman’s space, but do not corrleate with degree of inflammation.
- Inflammation does correlate with glomerular lesions and with active disease markers.
- Associated with worse prognosis

Therapeutic Trials

- Only limited numbers of randomized, controlled trials.
- No true measure of disease activity, so studies rely on measures of renal disease.
- Inconsistent measurement criteria.
- Varying degrees of blinding.
- Varying lengths of study.

Therapy: WHO Class II

- Good prognosis (find Lee et al 1984)
- Can treat with steroid monotherapy or even no therapy unless progression to more advanced class seen.

Therapy: WHO Class III

- If < 25% glomerular involvement, > 95% 5-year renal survival. No specific therapy required.
- If 40-50% glomerular involvement or more severe focal disease (necrosis, crescents, nephrosis, hypertension), prognosis like that of Class IV.

Therapy: WHO Class IV

- Most studies show that prednisone plus cytotoxic agents are superior to prednisone alone.
- Some investigators contend that prednisone monotherapy is shown to be equally effective in short term
- Cyclophosphamide generally shown to be superior to azathioprine as cytotoxic agent.

Therapy: WHO Class IV (cont.)

- Cyclophosphamide given as monthly pulse i.v. therapy believed to be less toxic than daily oral therapy.
- Maintenance therapy may reduce the risk of relapse.
- Pulse oral cyclophosphamide is presently being investigated.

Therapy: WHO Class IV (cont.)

- Bensal and Beto, 1997: Meta-analysis looking at 19 prospective controlled trials (440 pts) from 1970-1995.
- Did not to search for unpublished studies.
- Compared prednisone alone to prednisone + cytotoxic agents.
- Used ESRD and mortality as outcome measures.

Therapy: WHO Class V

- Some have suggested following protocols for idiopathic membranous GN.
- High-dose therapy (prednisone, cyclophosphamide, cyclosporine) used for elevated Cr or severe nephrosis. 10-yr renal survival rate = 93% reported.
- Poor prognostic indicators: African-American, hypertension, elevated Cr, high proteinuria.

Therapy: WHO Class V (cont.)

- Sloan *et al.* (1996): retrospective study, prednisone monotherapy with ?? Renal survival rate.
- Cyclosporine transiently reduced proteinuria, which

Therapy: WHO Class V (cont.)

HA Austin et al. (abst) JASN, 7:1328, 1996

	Prednisone Alone qod (n=8)	P + Cyclosporine < 5 mg/kg/d (n=5)	P + i.v. Cyclophosphamide 0.5-1.0 g/m^2 qom (n=6)
Proteinuria < 2 g/24 h	4/8	4/5	5/6
>20% rise in GFR	2/8	2/5	2/6
>20% fall in GFR	2/8	1/5	0/6
Relapse of proteinuria	1/4	4/4	1/6

Therapy: WHO Class VI

- Risk/benefit ratio of high-dose immunosuppresion unacceptable.
- Normal near-ESRD therapies, evaluation for renal replacement therapy are recommended.

Future Directions

- Immunology: Further elucidation of the role of the nucleosome and its antigens. Understanding of the defects in apotosis which may initate the autoimmune reaction.
- Therapeutics: Large double-blinded prospective randomized trials. Pulse i.v. versus oral regimens. Long-term outcomes.

References

- Adler, SG, AH Cohen, and RJ Glassock. Secondary glomerular diseases. Chapter 31 in Brenner, BM and FH Rector (eds.) *The Kidney, 5th edition, © 1996,* pp 1498-1568.
- Berden, JHM. Lupus nephritis. *Kidney Int*. **52**:538-558, 1997.
- Kashgarian, M. Lupus nephritis: lessons from the path lab. *Kidney Int*. **45**:928-938, 1994.
- Kramers, C, et al. Anti-nucleosome antibodies complexed to nucleosomal antigens show anti-DNA reactivity and bind to rat glomerular basement membrane in vivo. *J. Clin. Invest*. **94**:568-577, 1994.
- USRDS web page. http://www.med.umich.edu/usrds/

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References (cont.)

- Hahn, Bevra Hannahs. Mechanisms of Disease: Antibodies to DNA. *N Eng J Med*, **338**(19), 1998, pp1359-1368.
- Bach JF, Koutouzov. Immunology: New Clues to systemic lupus. *Lancet*, **350**(4S), pp11SIII, 1997.
- Studitsky, Vasily M.; Kassavetis, George A.; Geiduschek, E. Peter; Felsenfeld, Gary. Mechanism of Transcription Through the Nucleosome by Eukaryotic RNA Polymerase. *Science*, Volume **278**(5345) December 12, 1997 pp 1960-1963